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1290075

THE UNITED STATES OF AMERICA

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United States Patent and Trademark Office

February 28, 2005

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APPLICATION NUMBER: *60/541,590*
FILING DATE: *February 04, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US05/03780*

Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

PTO/SB/16 (01-04)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV362100130US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Americo Aniello	Migliaccio	Owings Mills, MD

Additional inventors are being named on the one separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

Method of Three-Dimensional Video-Oculography

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number:

OR

☑ Firm or Individual Name	Johns Hopkins University				
Address	100 N. Charles Street				
Address	5th Floor				
City	Baltimore	State	MD	Zip	21201
Country	USA	Telephone	410-516-8300	Fax	410-516-5113

ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 36 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☐ Other (specify)

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees.

☐ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number:

☑ Payment by credit card. Form PTO-2038 is attached.

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.

☒ Yes, the name of the U.S. Government agency and the Government contract number are: DC006216, DC002390

Respectfully submitted,

SIGNATURE Leigh A. Penfield

TYPED or PRINTED NAME Leigh A. Penfield

TELEPHONE 410-516-8300

Date 04-FEB-04

REGISTRATION NO. 37,050 *(if appropriate)*

Docket Number: 4001

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PROVISIONAL APPLICATION COVER SHEET
Additional Page

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Docket Number 4001

INVENTOR(S)/APPLICANT(S)		
Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
Charles Coleman	Della Santina	Towson, MD
Hamish Gavin	MacDougall	Woolloomooloo, Australia

Number _____ of _____

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

CERTIFICATE OF EXPRESS MAILING

EXPRESS MAILING LABEL NO.

EV362100130US

I hereby certify that this correspondence (along with any papers referred to as being attached or enclosed) is being deposited with the United States Postal Service as Express Mail, Post Office to Addressee with sufficient postage in a **Flat Rate** envelope addressed to MS Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below:

04-FEB-04

DATE of Signature
And of Mail Deposit

Cheryl Maxwood

Signature

Johns Hopkins University
Licensing & Technology Development

Report of Invention Disclosure Form (ROI)

This form is to be completed and submitted to the JHU office of Licensing and Technology Development (LTD) by anyone who believes they have developed a new invention. The purpose of this form is to enable LTD to evaluate whether legal protection to the invention will be sought and/or commercialization pursued. Please submit this form with all inventor(s) and Department Director(s) signatures. Visit the LTD web site at http://jhu.edu/technology/roi.html **for HTML and Word downloadable formats of this form.**

INVENTION INFORMATION

Title of Invention: [Title should be sufficiently descriptive to identify the invention yet not reveal unique unpublished details.]

Method of three-dimensional video-oculography

Lead Inventor Information: [The Lead Inventor is the primary contact person for LTD on all matters associated with this Report of Invention, including processing, patent prosecution and licensing. For reasons of administrative efficiency, it is the responsibility of the Lead Inventor to keep all other JHU inventors named on this Report of Invention informed of the status of such matters.]

Name of Lead Inventor: Migliaccio, (Last) Americo (First) Aniello (Middle) PhD (Degree)

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Social Security Number:

Are you a Howard Hughes Medical Institute employee or investigator? ☐ Yes ☒ No

Are you a Kennedy Krieger Institute employee or investigator? ☐ Yes ☒ No

Additional inventors: ☒ Yes ☐ No If yes, please complete Additional Inventors section for each inventor.

LTD Internal Use Only: REF- 4401 TLA _____ Field of Use _____

ADDITIONAL INVENTOR(S)

Please copy this page for additional inventors as necessary

Name of Inventor: Della Santina, (Last) Charles (First) Coleman (Middle) MD PhD (Degree)

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Are you a Howard Hughes Medical Institute employee or investigator? ☐ Yes ☒ No
Are you a Kennedy Krieger Institute employee or investigator? ☐ Yes ☒ No

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Citizenship: AUSTRALIAN Social Security Number:

Are you a Howard Hughes Medical Institute employee or investigator? ☐ Yes ☒ No
Are you a Kennedy Krieger Institute employee or investigator? ☐ Yes ☒ No

JHU REF: 4401

INVENTION DESCRIPTION

Describe the invention completely, using the outline given below. Please provide an **electronic copy** of the invention disclosure document, references, and abstracts in Windows format on CD-ROM or floppy disk if possible

1. **Brief Description of the Invention** [Please provide a non-confidential summary of the invention that can be used for marketing purposes. Unique details that are published (or will be published imminently) may also be included.]

We describe a novel, inexpensive method and apparatus for real-time measurement of binocular three-dimensional rotational eye position and velocity. The method employs consumer-grade digital video cameras to track an array of three fluorescent non-collinear markers affixed to each eye. A software element uses the positions of these markers before and after an eye rotation to construct a rotation matrix describing the eye rotation. The mathematical computation used to determine the rotation matrix is conceptually simpler and computationally more efficient than methods previously described, allowing generation of binocular three-dimensional eye position in real-time during image acquisition. When tested *in vitro*, the method had a >94% accuracy for eye positions within 20° of center. We compared this method of video-oculography (VOG) to the scleral search coil technique by measuring three-dimensional eye position simultaneously using scleral search coils and VOG in a chinchilla. The difference between the two methods was <5%. A second embodiment of the invention employs the same technique with faster cameras at higher resolution, yielding improved performance at increased cost.

SOFTWARE –Does this disclosure include a software element or software is implemented in the invention ☒ Yes ☐ No
If yes, please complete the Software Information Sheet which can be found at: _____
BIOLOGICAL MATERIAL – Does this disclosure include biological material, ☐ Yes ☒ No
If yes, please attach a list of materials for reference. A Tangible Property Report of Invention form may be completed if the disclosure is biological materials only. You can find this form at: http://www.hopkinsmedicine.org/lbd/otl/

2. **Problem Solved** [Describe the problem solved by this invention]

Precise and accurate measurement of eye rotation is essential for clinical evaluation and scientific study of vestibular (balance) and oculomotor (eye movement) disorders. However, most currently available measurement systems only measure 2 of the 3 dimensions of eye rotation (horizontal and vertical, but not torsional). Available three-dimensional systems are complex, and most require post-hoc processing to compute torsion. Those few that provide real-time measurement of eye torsional position are prohibitively expensive for many applications. There is a need among those who study and treat vestibular and oculomotor disorders for inexpensive, portable, real-time, binocular, three-dimensional eye movement measurement.

JHU REF: 4401

4401

SOFTWARE IMPLEMENTATION FORM

This form is to be completed and submitted with the JHU Report of Invention (ROI) and Assignment Form to the JHU office of Licensing and Technology Development (LTD) when there is a software element or software is implemented in the invention to which this form is attached. Visit the LTD web site at (Web page Here) for Word, ((PDF?)), and ((HTML?)) downloadable formats of this form.

1. Scope of Work [Is the work original? Is it created within the scope of your employment at JHU? Please explain the circumstances of program's development]

The work is original and was created within the scope of our employment. The software system was developed in order to measure the vestibulo-ocular reflex (VOR) in chinchillas. VOR measurements require accurate measurements of 3D eye position. Commercially available systems do no measure in 3D, do not measure in real-time or are prohibitively expensive.

2. Software Developers [Please list any developers of the software if different from invention]

The software is within the scope of the invention.

None ☐

3. Software Derivation [If software is a derivative of an existing work, please explain the original work's source and the modification]

The software is an original work.

None ☐

4. Third Party Content [Identify any third party content or other elements and their source included in the software]

We used standard modules from National Instruments Inc. library of software modules included LabVIEW G, NI-IMAQ Vision and NI-IMAQ for IEEE 1394 Cameras.

None ☐

5. Brief Software Description [Please characterize how robust and user friendly the work is.]

The software was programmed using the LabVIEW G visually-oriented software language. It makes use of standard software modules from the LabVIEW G libraries, including NI-IMAQ Vision and IEEE 1394. The software is driven by a graphical user interface that is robust and easy to use (taking about 10 minutes to learn for a new user) but designed to maintain maximum functionality.

3. Novelty [Identify those elements of the invention that are new when compared to the current state of the art]

We describe a novel method, apparatus and software program for real-time, binocular measurement of three-dimensional eye position using inexpensive, consumer-grade video cameras to track an array of markers on a piece of plastic film affixed to the cornea. To increase contrast between the markers and unwanted corneal reflections, the markers are fluorescent and illuminated with a UV light source which is either outside the camera's range of spectral sensitivity or filtered out using a UV cut filter or yellow pass filter. This novel lighting technique allows us to obtain images minus the light source. The three-dimensional eye rotation necessary to move a marker array from an initial eye position to a final eye position is calculated using a novel mathematical method that is simpler and more efficient than others described in the literature (Clarke et al., 2002; Nakayama, 1974; Ott et al., 1990). Because this system uses commercial–grade cameras that transmit data over a standard bus (IEEE-1394 FireWire), it can be implemented on a laptop computer without the use of any special or expensive hardware. This portability is a significant and novel advantage.

4. Potential Commercial Use – [What products can be produced with this invention.]

Eye movement systems used in most laboratories, such as scleral search coil systems and most video-oculography systems, are prohibitively expensive and require substantial technical expertise to use and maintain. In contrast, our system can be packaged as a low cost and easily portable alternative.

Although we predominantly use the system for measurements in animals, it is easily extended to humans. Human eye movement measurement systems are commonly used in clinical evaluation of patients with disorders of the inner ear and nervous system and in scientific research regarding these disorders. Additional potential applications include measurement of eye position and movements to convey information to a computer system for data entry, for command and control (e.g., navigation of computer-controlled equipment), for communication, and for enhancement of virtual reality-based displays.

5. Commercialization - List any companies that you feel may be interested in this technology or are doing similar research. Indicate how the invention complements the company's existing technology. If known, provide the names of any companies (and a contact person) who have contacted you regarding your research related to the invention.

1. SensoMotoric Instruments GmbH, Germany, http://www.smi.de
2. Oxford instruments, http://www.oxinst.com/MDCAPP288.htm
3. Skalar Medical, http://www.skalar.nl/
4. Chronos Vision GmbH, http://www.chronos-vision.de/
5. Tobii technology, http://www.tobii.se/
6. SR Research, Ltd. www.eyelinkinfo.com
7. Seeing machines, Inc. www.seeingmachines.com
8. LC Technologies, Inc. www.eyegaze.com
9. Smart Eye AB, www.smarteye.se
10. Applied Science Laboratories, www.a-s-l.com
11. Eyetools, inc. www.eyetools.com

☐ No company interest known at this time.

Keywords – Please circle the categories and keywords that accurately describe the present invention.

JHU REF: 4401

CHEMICAL
- ☐ Additives
- ☐ Alternative Energy
- ☐ Antioxidants
- ☐ Batteries
- ☐ Catalyst
- ☐ Coal Conversion
- ☐ Coatings
- ☐ Effluent Treatment
- ☐ Elastimers
- ☐ Electrochemistry
- ☐ Exhaust Treatment
- ☐ Foams
- ☐ Food Chemistry
- ☐ Fuel Cells
- ☐ Gas Conversion
- ☐ Gels
- ☐ Monomers
- ☐ Oxidation
- ☐ Petroleum
- ☐ Photochemistry
- ☐ Polymers
- ☐ Remediation
- ☐ Solvents

DIAGNOSTIC
- ☐ Antibody
- ☐ Assay
- ☐ Biochip
- ☐ Contrast Agent
- ☐ Detection
- ☐ DNA Probe
- ☐ Elisa
- ☐ Imaging
- ☐ Immunoassay
- ☐ In Situ
- ☐ Marker
- x **Measurement**
- ☐ MRI
- ☐ Point of Use
- ☐ Radioisotope
- ☐ Transgenic
- ☐ Ultrasound

GENOMICS
- ☐ Allele
- ☐ Bioinformatic
- ☐ cDNA
- ☐ Epidemiology
- ☐ EST
- ☐ Gene
- ☐ Homologue
- ☐ Isogene
- ☐ Library
- ☐ Mutation
- ☐ Pharmacogenomics
- ☐ Polymorphism
- ☐ Positional Cloning
- ☐ Proteomics
- ☐ Receptor
- ☐ RNA
- ☐ Target Validation

MEDICAL DEVICE
- ☐ Delivery
- x **Diagnosis**
- ☐ Imaging
- x **Measurement**
- x **Optical**
- ☐ Safety
- ☐ Surgical
- ☐ Treatment

RESEARCH TOOL
- x **Animal Model**
- ☐ Antibody
- ☐ Cell Line
- ☐ Culture
- ☐ Directed Evolution
- ☐ DNA Probe
- ☐ DNA/RNA Sequencing
- ☐ DNA/RNA Synthesis
- ☐ Electrophoresis
- ☐ Elisa
- ☐ Enzyme
- x **Equipment**
- ☐ Expression System
- ☐ Immunoassay
- ☐ Label
- ☐ PCR
- ☐ Protein Sequencing
- ☐ Protein Synthesis
- ☐ Reagent
- ☐ Spectroscopy
- ☐ Tissue Culture
- ☐ Vector

SCREENING
- ☐ Assay
- ☐ Biochip
- ☐ Combinatorial Biology
- ☐ Combinatorial Chemistry
- ☐ Detection
- ☐ HTS
- ☐ Phage Display
- ☐ Screen
- ☐ Target

THERAPEUTIC
- ☐ Analgesic
- ☐ Anesthetic
- ☐ Angiogenesis
- ☐ Antibiotic
- ☐ Antibody
- ☐ Antifungal
- ☐ Antiinflammatory
- ☐ Antisense
- ☐ Antiviral
- ☐ Apoptosis
- ☐ Cell Signaling
- ☐ Cell Therapy
- ☐ Disease Model
- ☐ Drug Delivery
- ☐ Drug Design
- ☐ Fertility
- ☐ Gene Therapy
- ☐ Hormone
- ☐ Immunotherapy
- ☐ Natural Product
- ☐ Peptides
- ☐ Pro-drug
- ☐ Proteins
- ☐ Small Molecule
- ☐ Tissue Engineering
- ☐ Transplant
- ☐ Vaccine
- ☐ Virus
- ☐ Wound Healing

DISEASES
- ☐ Aging
- ☐ Blood
- ☐ Cancer
- ☐ Cardiovascular
- ☐ Dermatologic
- ☐ Endocrine
- ☐ Gastrointestinal
- ☐ Genitourinary
- ☐ Hepatic
- ☐ Immune
- ☐ Infectious
- ☐ Metabolic
- ☐ Musculoskeletal
- x **Neurological**
- ☐ ObGyn
- ☐ Ophthalmological
- x **Otolaryngologic**
- ☐ Pediatric
- ☐ Psychiatric
- ☐ Respiratory

ADDITIONAL KEY WORDS:

_____

_____

_____

STAGE OF DEVELOPMENT
- ☐ Unspecified
- ☐ Discovery
- ☐ Preclinical
- x **Prototype**
- ☐ Phase I
- ☐ Phase II
- ☐ Phase III
- ☐ NCE

7. Detailed Description of the invention - On a separate page(s), attach a detailed description of how to make and use the invention. The description must contain sufficient detail so that one skilled in the same discipline could reproduce the invention. Include the following as necessary:

1- data pertaining to the invention;
2- drawings or photographs illustrating the invention;
3- structural formulae if a chemical;
4- procedural steps if a process
5- a description of any prototype or working model;

In general, a manuscript that has been prepared for submission to a journal will satisfy this requirement.

JHU REF: 4401

8. Workable Extent/Scope [Describe the future course of related work, and possible variations of the present invention in terms of the broadest scope expected to be operable; if a ***compound,*** describe substitutions, breadth of substituents, derivatives, salts etc., if ***DNA or other biological material***, describe modifications that are expected to be operable, if a ***machine or device***, describe operational parameters of the device or a component thereof, including alternative structures for performing the various functions of the machine or device]

This method tracks a marker array that is affixed to each eye. The marker array can be affixed directly onto the cornea of animals. Alternatively, one can tattoo or inscribe the markers on the eye surface. For human applications, the marker array could be drawn on the eye or embedded into a contact lens.

This method uses a light source that has a different spectral wavelength versus the light emitted by the fluorescent marker array. Corneal reflections of the light source may therefore be filtered out using an optional optical cut filter, increasing image contrast and simplifying image analysis. In the current embodiment, a UV light source (either UV fluorescent bulb or light-emitting diode [LED]) is used. A similar approach could be implemented using, for example, an infrared light source to illuminate a marker array that emits visible light.

LEDs can optionally be used to help align the center of the camera image with the center of the eye. This can be implemented by fixing 2 or more UV (or IR, or visible) LEDs at equal distances from and at equal angles around the camera lens . The average position of the point source reflections from these LED's will be at the center of the image only when the camera is aligned with the center of curvature for the cornea. Since the center of curvature and the center of rotation of the eye are fairly coincident for species with near spherical eyes (such as chinchilla, rabbit, mouse, guinea pig etc.) this method provides a simple method to establish camera alignment.

Although the initial embodiment of the design employs inexpensive cameras to achieve 30 samples/sec eye tracking at very modest cost, we have also adapted this method to use faster, higher-resolution cameras allowing real-time 3D binocular oculography at 120 samples/sec without loss of special resolution, and at 240 samples/second and higher by reducing image resolution. The "plug and play nature" of the IEEE1394 'FireWire' standard allows one to easily incorporate faster, higher-resolution cameras as they become available. For example, the FireWire 800 (IEEE-1394b) standard provides double the bandwidth of FireWire 400 (IEEE-1394). Further improvements in performance can be achieved by modifying camera hardware and firmware so that 8 bit images are converted to 1 bit images (onboard thresholding), or to the x,y pixel location of each marker before being transmitted over the bus.

At present only ~10-20 laboratories in the world are capable of accurately measuring eye movement response to a high acceleration head rotation. Research performed by these laboratories indicates that measurement of vestibular function using high-speed eye tracking during high-acceleration head rotations has significant advantages over currently available tests for clinical assessment of dizzy patients. Our method can be integrated into a comparatively very inexpensive, automated head movement delivery and eye movement response vestibular testing system for research and clinical applications. Such a system would have a potentially large world market. Over 90 million Americans suffer from dizziness; it is the ninth most common reason adults visit a primary care doctor. Thirty-four percent of Americans age 65-74 suffer from dizziness significant enough to limit their activities of daily life, making it the third most common medical complaint among this group. Dizziness is the most common complaint in patients 75 years and older (Hoffman 1999, NIH Task Force 1996).

9. References [Please cite relevant journal citations, patents, general knowledge or other public information related to the invention and distinguish between references that (A) contain a description of the current invention from those that (B) contains background information.]

See reference list in attached paper. In addition to those, please also see these recent relevant publications:

1: Clarke AH, Ditterich J, Druen K, Schonfeld U, Steineke C. Using high frame rate CMOS sensors for three-dimensional eye tracking. Behav Res Methods Instrum Comput. 2002 Nov;34(4):549-60. PMID: 12564559 [PubMed - indexed for MEDLINE]

2: Frens MA, van der Geest JN. Scleral search coils influence saccade dynamics. J Neurophysiol. 2002 Aug;88(2):692-8. PMID: 12163522 [PubMed - indexed for MEDLINE]

3: Van der Geest JN, Frens MA. Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. J Neurosci Methods. 2002 Mar 15;114(2):185-95. PMID: 11856570 [PubMed - indexed for MEDLINE]

4: Hoffman RM, Einstadter D, Kroenke K, Am J Med 1999 Nov;107(5):468-78

5: Task Force on the National Strategic Res. Plan. Balance and the vestibular system. NIH. Bethesda MD 1989:73 National Health interview supplement on aging 1996

Patent No.	Inventor/s	Short description
6,299,308	Veronka et al.	Low cost infra-red illuminated 1-2D eye tracking system using photodiode detectors.
6,152,564	Ober et al.	Infra-red illuminated 2D eye tracking systems –infra sensor and light source mounted on nose.
5,070,883	Kasahara et al.	Head mounted TV cameras track the 2D position of the pupil.
4,815,839	Waldorf	Enclosed spherical goggles with infra-red light source and mounted camera.
4,145,122	Rinard et al.	Infra-red illuminated 2D eye tracking system uses infra-red sensitive 32x32 photo-sensor array.

☐ No references available at this time.

RESEARCH SUPPORT INFORMATION

Indicate ALL contributions to the development of the invention in terms of personnel, money, materials and facilities etc. Check each funding source that applies to this invention:

☐ None ☒ Federal Sponsor(s) ☐ University Funding ☐ Commercial Funding ☐ Other

For each funding source, provide the below information. Additionally, if "Commercial" or "Other" Funding was used, please attach a copy of each such award notice.

Granting/Funding Source	Award/Contract Number	Title of Grant	% of Support	Copy Attached
NIH/NIDCD	K08-DC006216	Elect. stim. to restore vestibular function		☐
NIH/NIDCD	R01-DC2390	Physiology of vestibular compensation		☐
				☐
				☐
				☐

AGREEMENT SUPPORT INFORMATION

Were any materials, equipment or software under a Special Agreement, such as Material Transfer agreements, purchase agreements, sponsored research agreements, or the like used? ☐ Yes ☒ No If yes, please provide the following information for each item and attach a copy of the Agreement.

Source of Materials	Materials	Copy Attached
		☐
		☐
		☐

DISCLOSURES OF THE INVENTION

Check any prior disclosures or anticipated disclosures, either written or oral, of the Invention:

☐ Abstract(s) ☒ Publication(s) ☐ Seminar(s) ☐ Presentation(s) ☐ Other ☐ None

For each disclosure, provide the following information as appropriate in the space below:

- If **PUBLISHED**, include all journal citations and attach a reprint.
- If **NOT YET PUBLISHED**, attach a copy of the abstract or manuscript and the anticipated publication date.
- For any other written or oral disclosure, provide the names, addresses and affiliation of anyone to whom you have disclosed the Invention and the date of any disclosure.
- For each disclosure please provide an electronic copy, as appropriate.

Title of Disclosure	Date of Disclosure	Copy Attached
		☐
Manuscript submitted to Journal of Neuroscience methods on 01/31/2004		☒
Inexpensive system for real-time 3-dimensional video-oculography using a fluorescent marker array.		☐
Migliaccio AA, MacDougall HG, Minor LB, Della Santina CC.		☐

ACKNOWLEDGMENT, CERTIFICATION and ASSIGNMENT OF INVENTION

In order for this Report of Invention to be complete and processed by LTD, it must be signed and dated by:

(1) the JHU Department Director for each JHU department involved with the development of this invention (SECTION A), and,

(2) ALL Inventors (SECTIONS B and C), including those Inventors not subject to The Johns Hopkins University Intellectual Property Policy. Each Inventor must complete only one of Sections B or C (See explanations in the following sections).

(3) Please duplicate Sections A, B and/or C as needed for proper completion with ALL appropriate signatures.

SECTION A. JHU SCHOOL and DEPARTMENT DIRECTOR'S ACKNOWLEDGEMENT

I have read and understood this Report of Invention.

JHU Department Director Signature	Americo A. Migliaccio, PhD Typed or Printed Name Otolaryngology – Head & Neck Surgery JHU Department and School	Date 02/02/2004
JHU Department Director Signature	Charles C. Della Santina, MD PhD Typed or Printed Name Otolaryngology – Head & Neck Surgery JHU Department and School	Date 02/02/2004
JHU Department Director Signature	Typed or Printed Name JHU Department and School	Date

JHU REF: 4401

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JHU Inventor Signature	Charles. C Della Santina Typed or Printed Name	Date 02/02/2004 % of Contribution: 50%
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Inexpensive system for real-time 3-dimensional video-oculography using a fluorescent marker array

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Abstract

We describe a novel, inexpensive method for real-time measurement of binocular three-dimensional eye position. The method employs consumer-grade digital video cameras ("webcams") to track an array of three fluorescent non-collinear markers affixed to each eye. The positions of these markers before and after an eye rotation were used to construct a rotation matrix describing the eye rotation. The mathematical computation used to determine the rotation matrix is conceptually simpler and computationally more efficient than methods previously described, allowing generation of binocular three-dimensional eye position in real-time during image acquisition. When tested *in vitro,* the method had a >94% accuracy for eye positions within 20° of center. We compared this method of video-oculography (VOG) to the scleral search coil technique by measuring three-dimensional eye position simultaneously using scleral search coils and VOG in a chinchilla. The difference between the two methods was <5%.

Keywords: three-dimensional, 3-D, video-oculography, eye position, UV illumination, fluorescent marker array.

Introduction

Precise and accurate measurement of eye rotation is central to vestibulo-ocular research. The eye can rotate in three dimensions: horizontally, vertically and torsionally (about the line of sight). The "gold standard" method for measuring three-dimensional eye position is the scleral search coil technique (Robinson, 1963; Collewijn et al., 1985). In animal experiments, the search coils can either be implanted (Paige and Tomko, 1991; Minor et al., 1999) or glued to the eye (Gilchrist et al., 1998). Implantation of search coils can restrict eye movements due to conjunctival scarring and inflammation or coil lead tension. These problems become increasingly significant when coils are implanted in rodents and other species with small eyes, for which even the usually negligible contribution of coils to ocular moment of inertia may become important (Stahl et al., 2000). Depending on surgical technique, coil implantation can also damage extraocular muscles and their pulleys, further distorting eye movements (Demer et al., 1995). Gluing coils to the frontal surface of the eye minimizes the risk of restriction due to scarring; however, glued coils and their leads can impede eye movement range by impacting the lids and canthi. Repeated impact of the coils against lid margins can dislodge the coils, limiting the duration of experiments. Whether implanted or glued, scleral search coils require uniform, stable magnetic fields for transduction of eye rotation. These fields can be distorted by metallic objects and by currents flowing in equipment nearby.

The drawbacks of the scleral coil technique have prompted efforts to develop video-oculographic (VOG) systems for measurement of three-dimensional eye position. Such systems are gaining wider acceptance. Horizontal and vertical eye position can be determined by tracking the pupil or a corneal reflection (Stahl et al., 2000; Kaufman, 2002). To determine ocular torsion, most currently available VOG systems either track

landmarks on the eye (Nakayama 1974; Parker et al., 1985; Yamanobe et al., 1990; Ott et al., 1990) or employ some variation of the polar cross correlation method, which involves measuring and tracking changes in iral contrast along a circular sampling path (Hatamian and Anderson, 1983; Vieville and Masse, 1987; Clarke et al., 1991; Moore et al., 1991). In humans, pronounced iral striations make the polar cross correlation method practical. In animals that do not have pronounced iral striations, such as the chinchilla, rabbit, guinea pig and other rodents, it is more effective to track attached landmarks.

We describe an inexpensive technique for real-time measurement of three-dimensional eye position using consumer-grade digital video cameras to track an array of three 1 x 1 mm markers on a piece of plastic film affixed to the cornea. To increase contrast between the markers and unwanted corneal reflections, the markers were fluorescent and illuminated with a UV light source outside the camera's range of spectral sensitivity. The marker array was glued to the frontal surface of each cornea and typically remained attached for >4 hours. The three-dimensional eye rotation necessary to move a marker array from an initial position to a final position was calculated using a mathematical method that is simpler and more efficient than others described in the literature (Nakayama, 1974; Ott et al., 1990). We used inexpensive, consumer-grade "webcam" digital video cameras and LabVIEW G (National Instruments, Austin, TX) to simplify software development. Binocular three-dimensional eye positions were computed and displayed in real-time. We validated the system *in vitro* using a Fick gimbal and *in vivo* by comparing eye movement measurements made simultaneously using both scleral search coils and VOG.

Materials and Methods

Fluorescent Marker Array and Light Source

We fabricated the fluorescent marker array using plastic film laminated on paper saturated with fluorescent yellow ink. The film was opaque except for 3 transparent 1 x 1 mm windows separated by 1 mm and arranged in a 45° right triangle. A small amount of cyanoacrylate was used to improve adhesion of the marker array to the eye (Hess and Dieringer, 1991). In order to measure vestibular-mediated eye movements in the absence of vision, we made these marker arrays large enough to occlude the pupil (elliptical with ~4 mm diameter). A diffuse ultraviolet light source (360 nm peak, 9 Watt, FPX7BLB, Ushio Inc., Japan) illuminated the array (Figure 1). Alternatively, 380 nm UV LEDs (SSL-LX5093SUVC, Lumex Inc.) are also suitable. Depending on the spectral sensitivity of the specific camera used, a UV cut filter (SKYLIGHT 1B Hoya, Japan) or a yellow pass filter (K2 yellow filter Hoya, Japan) can be used to improve contrast. No filter was necessary with the webcams we used, because their color CCD is already less sensitive to UV than most monochrome image sensors.

VOG Processing

The VOG system was installed on a Pentium IV 2.4GHz 1GB RAM PC running Windows 2000. IEEE 1394 Firewire webcams (PYRO1394 WebCam, ADS Technologies, USA) were used to acquire 640 x 480 pixel B&W (8-bit) images at 30Hz for each eye. National Instruments LabVIEW 7.0, NI-IMAQ Vision 7.0.1 and NI-IMAQ for IEEE 1394 Cameras 1.5 standard modules were used to control camera settings such as contrast and brightness. Standard NI-IMAQ modules were used to change the image

threshold so that only the three markers were visible on a black background and to determine the center of each marker using a center of mass algorithm. Pixel size was calibrated using the known distance between markers.

Fourteen chinchilla eyes were dissected shortly after euthanasia and measured using calipers, revealing a mean globe diameter of 13.6 ± 0.6 mm. Assuming the eye is a sphere that rotates about its center and is centered on the camera's optical axis, and defining the center of the eye as the origin of a coordinate system, one can calculate the position in space of each marker. The rotation matrix uniquely describing the eye rotation required to move the three markers from one position to another is:

$$\text{Rotation Matrix} = \begin{bmatrix} X_{0current} & X_{1current} & X_{2current} \\ Y_{0current} & Y_{1current} & Y_{2current} \\ Z_{0current} & Z_{1current} & Z_{2current} \end{bmatrix} * \begin{bmatrix} X_{0ref} & X_{1ref} & X_{2ref} \\ Y_{0ref} & Y_{1ref} & Y_{2ref} \\ Z_{0ref} & Z_{1ref} & Z_{2ref} \end{bmatrix}^{-1}$$

where $$X_i = \sqrt{\left((eye\_radius\_in\_pixels)^2 - \left(Y_i^2 + Z_i^2\right)\right)}$$

The X-axis is naso-occipital (forward positive), the Y-axis is interaural (left positive) and the Z-axis is superior-inferior (up positive). The subscript *ref* refers to marker position before a rotation and defines the reference or zero rotational position of the eye. The subscript *current* refers to the marker positions in 3-D space after a rotation. Euler angles, rotation vectors and quaternions are calculated directly from the rotation matrix (Haslwanter, 1995; Migliaccio and Todd, 1999). Using 640x480 pixel cameras and magnification optimized so that the marker array range of motion filled the camera image frame, the absolute resolution of the system was <0.2°.

The above algorithm depends on alignment of the camera center with the center of the eye. Misalignment may be translational (camera pointing in proper direction, but not through eye center) or angular (camera through eye center, but not in proper direction). Each type of error can be corrected *post hoc* as long as the extent of misalignment is known. Translational misalignment can be corrected by redefining the image center so that rather than using the default (center pixel of the camera image), the image pixel that aligns with the center of the eye is defined as the origin. Angular misalignment can be corrected by multiplying each eye rotation matrix by the inverse rotation matrix describing camera position in eye coordinates.

Tracking of one or more of the markers may be lost when they move behind the eyelid or into a poorly illuminated region. After tracking loss due to marker occlusion and subsequent reacquisition of all markers identifying which marker is which becomes difficult. However, only one of 6 possible permutations gives the correct pairing of all 3 markers from one image to the next. We determined the correct pairing by calculating the summed square of marker travel distances for each permutation and accepting the permutation that resulted in the smallest value.

Binocular video analysis can be computationally intensive. We optimized our code to use NI-IEEE 1394 software interrupts, freeing the CPU for other processing until a new video image was acquired. Camera output was time-shifted to account for a 33 ms delay between camera shutter closure and arrival of the new image in PC memory.

Scleral Search Coil System

For each eye, two coils (2 mm diameter insulated copper, 80 turns, ~0.003 mg) were glued together with cyanoacrylate and positioned orthogonal to one another (Gilchrist et al., 1998). Lead wires from the coil pair were tightly twisted to avoid artifacts generated by the movement of loops in the lead wire within the magnetic fields. Lead connectors were kept fixed with respect to fields during calibration and during the experiment.

Three pairs of field-generating coils, each with a side length of 45 cm, were rigidly attached to a superstructure that moved with the animal. The three magnetic fields were mutually orthogonal and aligned with the X (naso-occipital), Y (interaural) and Z (superior-inferior) coordinate axes. The X, Y and Z fields oscillated at 100kHz, 50kHz and 75kHz, respectively. The three amplitude-modulated frequency signals induced in each coil were demodulated to produce three voltages proportional to the angles between each coil and each magnetic field (Remmel, 1984). A full description of the calibration and signal processing methods applied to these signals has been described elsewhere (Straumann et al., 1995; Migliaccio et al., 2003). The peak-to-peak noise at the output of the circuit was equivalent to an eye movement of 0.02°. All signals transducing motion of the head or the eye were passed through eight-pole Butterworth anti-aliasing filters with a corner frequency of 100Hz. Coil signals were digitized at a sampling rate of 1kHz.

In Vitro experiment - Fick gimbal and VOG

A marker array scaled to 4.5 times larger than the fluorescent marker array used *in vivo* was positioned 31 mm forward from the center of a Fick gimbal (equivalent to 4.5

times the radius of a chinchilla eye). A camera was placed 242 mm directly in front of the Fick gimbal center so that the image center aligned with the center of the gimbal. The gimbal was machined to be accurate to 0.1° and was rotated in 10° steps from -20° to +20° in all combinations of yaw, pitch and roll.

To quantify effects of *translational* misalignment, measurements were then repeated with the camera deliberately translated so that the difference between the gimbal center and image center was either 17% or 35% of the gimbal radius (equivalent to 1.1 mm or 2.2 mm off the center of a chinchilla eye). Measurements were again repeated with intentional *angular* misalignments of 1.3 ° and 2.5 ° (again equivalent to 1.1 mm or 2.2 mm off the center of a chinchilla eye).

In Vivo experiment – combined scleral search coils and VOG

We measured eye movements mediated by the vestibulo-ocular reflex in response to head rotations in a healthy normal chinchilla (*Chinchilla laniger*) to verify the accuracy of the VOG system. A head bolt was placed surgically under sevoflurane anesthesia for animal restraint during subsequent eye movement testing. The dorsal surface of the skull was exposed, both bullae were opened using an otologic drill, and a lightweight ceramic rod was positioned on the skull in the midline and embedded in a dental acrylic cap extending from one bulla to the other. The ceramic rod was oriented parallel to the animal's supero-inferior axis. The animal was placed into a plastic restraining device with one end containing a socket to hold the rod. The animal-restraining device was mounted on a gimbal structure that allowed any of the vestibular semicircular canals to be tilted into the earth-horizontal plane for rotational testing. The

gimbal structure was mounted on a servo-controlled rate table (model 130-80/ACT2000; Acutronic USA, Inc, Pittsburgh, Pa) that rotated about an earth-horizontal axis. All surgical and other animal care procedures were done in accordance with a protocol approved by the Animal Care and Use Committee of the Johns Hopkins University School of Medicine.

The animal was positioned with its head centered on the motor's rotating axis. Cameras were fixed to the test apparatus and positioned along the corneoretinal axis of each eye in its resting position (~70° off the naso-occipital axis in the horizontal plane). The medial and lateral canthi were both visible in the video image. Alignment was confirmed by temporary lid retraction sufficient to visualize the superior, inferior, nasal and temporal extent of the limbus and globe, and then retraction was reduced to the minimum necessary to image the marker array throughout the oculomotor range. Each eye received two drops of anaesthetic (proparacaine hydrochloride 0.5%) before the marker arrays and scleral search coils were affixed. The testing chamber was dark apart from the UV source, and the marker arrays occluded the pupils.

The animal was rotated at 0.5, 1, 2 and 5Hz with peak velocity 20°/s or 50°/s in the plane of each semicircular canal pair: yaw (horizontal canals), LARP (left anterior and right posterior canals) and RALP (right anterior and left posterior canals). The animal was also rotated about its naso-occipital axis (roll) and its interaural axis (pitch). The eye movements generated by the vestibulo-ocular reflex should be approximately equal in magnitude, but opposite in direction to the head rotation (Ewald, 1892; Merwin et al., 1989).

Results

In vitro experiment - Fick gimbal and VOG

Figure 2 shows the difference between the actual gimbal angle and the angle as measured by VOG. For horizontal, vertical and torsional Fick angles from –20° to 20°, the root mean square VOG error was 4.4%, 3.3% and 5.8%, respectively. For horizontal, vertical and torsional Fick angles from –30° to 30°, the root mean square VOG error was 3.8%, 3.4% and 7.3%, respectively.

For excursions within –20° to 20° of center with *translational* misalignment of the camera equal to 17% of the gimbal radius, the error in horizontal, vertical and torsional Fick components measured by VOG was 4.1%, 15.6% and 10.9%, respectively. For 34% misalignment, the VOG errors were 9.8%, 28.3% and 20.3%, respectively.

For excursions within –20° to 20° of center with *angular* misalignment of the camera equal to 1.3°, the error in horizontal, vertical and torsional Fick components measured by VOG was 7.9%, 20.0% and 11.5%, respectively. For 2.5° angular misalignment, the VOG errors were 19.2%, 43.6% and 52.9%, respectively.

In Vivo experiment – combined scleral search coils and VOG

The eye movement responses to yaw and roll head rotations (at 2 Hz with peak velocity of 50°/s) in head coordinates are shown in Figures 3A and 3B. To facilitate comparison between coil and VOG measurements, the horizontal, vertical and torsional components of eye velocity are plotted in separate panels. The horizontal head velocity is included in each panel in Figure 3A, and the torsional head velocity is included in each panel in Figure 3B. Despite the fact that derivation of eye positions from scleral coil

signals relies on completely independent mathematical processing, 3-D eye velocity measured using both methods matched closely. The root mean square difference in eye velocity measured using the coil and VOG method is <5%. During head rotational stimuli with frequencies ≤5 Hz, the average RMS difference between the two methods was 2.2%, 3.7% and 4.1% for the horizontal, vertical and torsional components of eye velocity, respectively. The noise of the VOG system was <5°/s peak in all dimensions. The phase difference of the eye movement response measured using coils and VOG was <2° for eye movements with frequency components ≤2 Hz, and <7° for eye movements with frequency components ≤5 Hz.

Being a lateral-eyed animal, the chinchilla's resting eye position is ~70° off the naso-occipital axis, so during purely roll *head* rotations, *eye* velocity had large vertical and torsional components in *eye* coordinates (camera coordinates). In one eye, the vertical and torsional eye velocity components were in phase with each other, whereas in the other eye they were in anti-phase. However, when the frame of reference was changed from eye to head coordinates, equivalence of the eyes' movement became apparent, as expected for eye movements mediated by the vestibulo-ocular reflex. The torsional eye velocity was large and comparable to head velocity, while horizontal and vertical eye velocity components were small.

Discussion

The VOG method we present accurately measures eye position during eye rotations with frequency components ≤2Hz. The resolution of the system is <0.2° peak and the differentiated velocity noise is <5°/s peak.

VOG and search coil techniques possess distinct sets of advantages and disadvantages. Implanting scleral search coils requires delicate surgery and can alter eye movements due to surgical trauma. Very fine wire can be used to make coils small, but then the experimental window of opportunity is limited, because the coils tend to break a few weeks after implantation. Apart from placement of a marker array on the eye (which could be incorporated into a standard contact lens for humans), VOG is non-invasive, and there are few concerns regarding restriction of normal eye movements. However, the VOG technique has several disadvantages. The head is usually fixed with respect to the camera, and head-free experiments on small animals would be difficult (although head-fixed VOG is well developed for humans). Spatial resolution is limited by the size of the video pixel, and as a consequence, quantization noise may be higher than with coils. Resolution can be improved somewhat by enlarging the percentage of the video image occupied by the marker array, but only to a limit, since the field of view must remain large enough to contain the marker array for extremes of eye position. Increased CCD resolution is also possible, though at increased cost and with increased computational overhead. Temporal resolution is also limited in the inexpensive system described here, which samples video images at 30 samples/s for each of two cameras (one per eye). We have also implemented a higher performance alternative system using high-speed industrial-grade CMOS Firewire cameras (Scorpion II, Point Grey Research, USA), at a

cost ~10X that of the "webcams" described above. Due to the "plug and play" nature of the Firewire bus standard, a 120Hz sample rate was achieved for each of two cameras running concurrently on the PC described earlier (for binocular VOG), with no change in spatial resolution or interface software. These more expensive cameras permit tradeoff of temporal and spatial resolution. For example, a sample rate of 240Hz was made possible by decreasing the image resolution by 50%.

The eye tracking technique we present relies upon a number of simplifications, including the assumptions that the eye rotates about a single point in space and that the eye is spherical. Most of our vestibular eye movement experiments require absence of visual input, so we purposefully position the opaque marker array over the pupil and iris so as to obstruct vision. If necessary, the marker array is small enough to be positioned non-occlusively. While one could forego the use of an affixed marker array and instead tattoo or etch markers onto the iral or scleral surface, a method to increase marker signal-to-noise ratio above that of corneal reflections, such as fluorescence used here, is helpful. Another possibility is the construction of a silicone scleral "contact lens," similar to those used in human studies (Robinson, 1963), with fluorescent markers embedded into it. With such an approach, this accurate, inexpensive VOG technique could also be used to measure real-time binocular three-dimensional eye position in humans.

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Figure legends

Figure 1. Fluorescent marker array on the left eye of a chinchilla. For this photograph, the eye was illuminated with visible light in addition to UV. Under normal testing conditions, only UV illumination is used, increasing the relative brightness of fluorescent markers.

Figure 2. The difference between the gimbal angle and the angle of the marker array as measured by VOG. For angular positions with horizontal, vertical and torsional components between -20-20° the VOG error was <5.8%

Figure 3. The eye movement responses to yaw and roll head rotations (at 2 Hz with peak velocity of 50°/s) in head co-ordinates are shown in figures A and B. The horizontal, vertical and torsional components of eye velocity are shown in separate panels. The horizontal head velocity is included in each panel in figure A and the torsional head velocity is included in each panel in figure B. The difference in eye velocity measured using the coil and VOG method is <5%.

Figure 1.

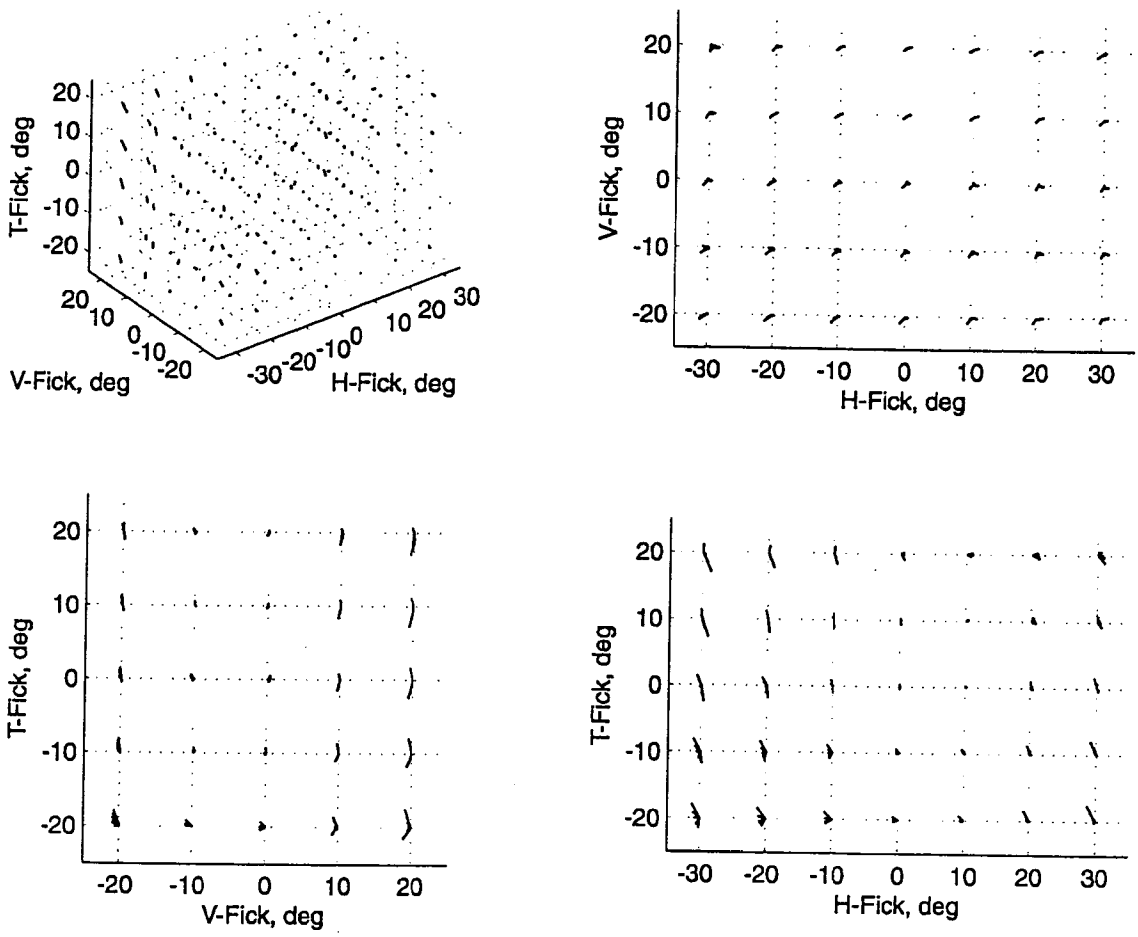

Figure 2.

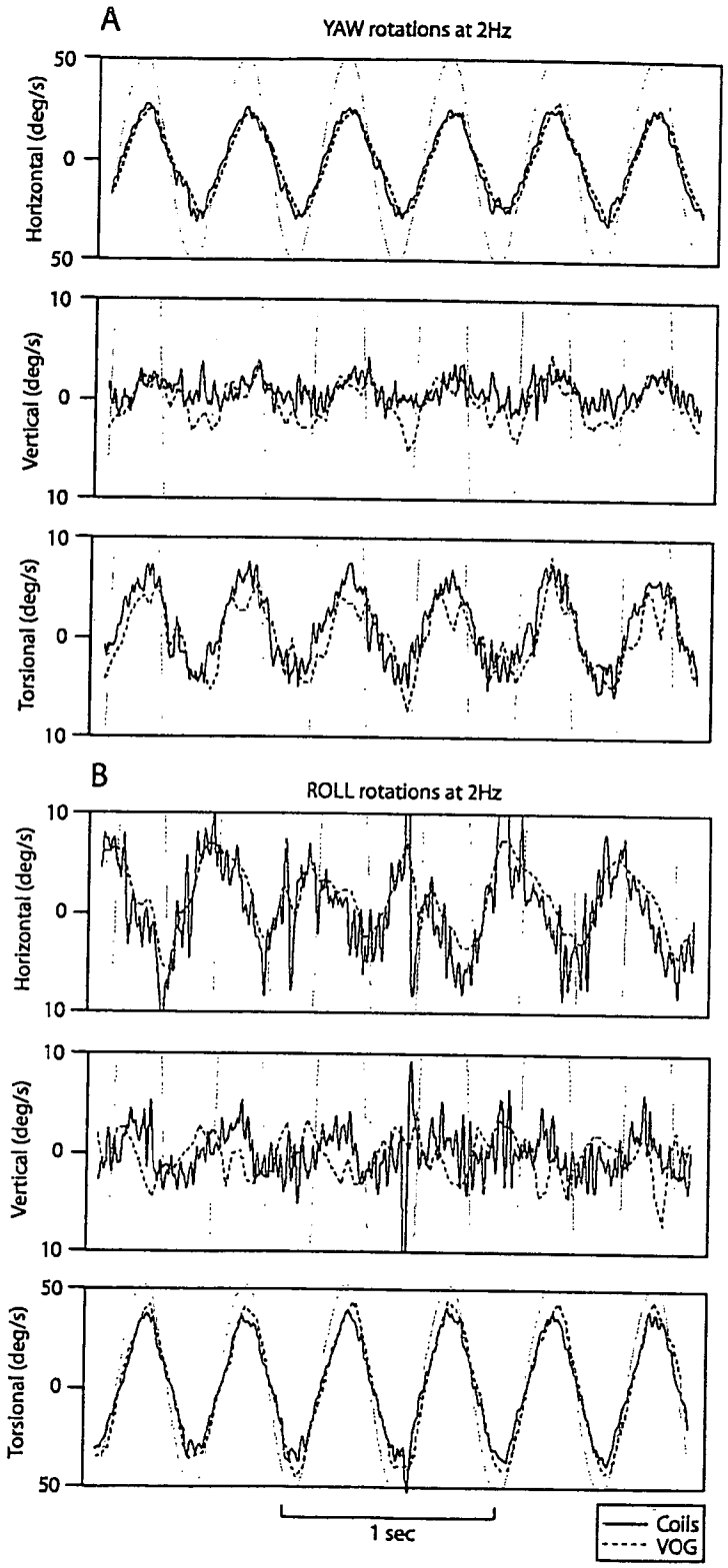

Figure 3.

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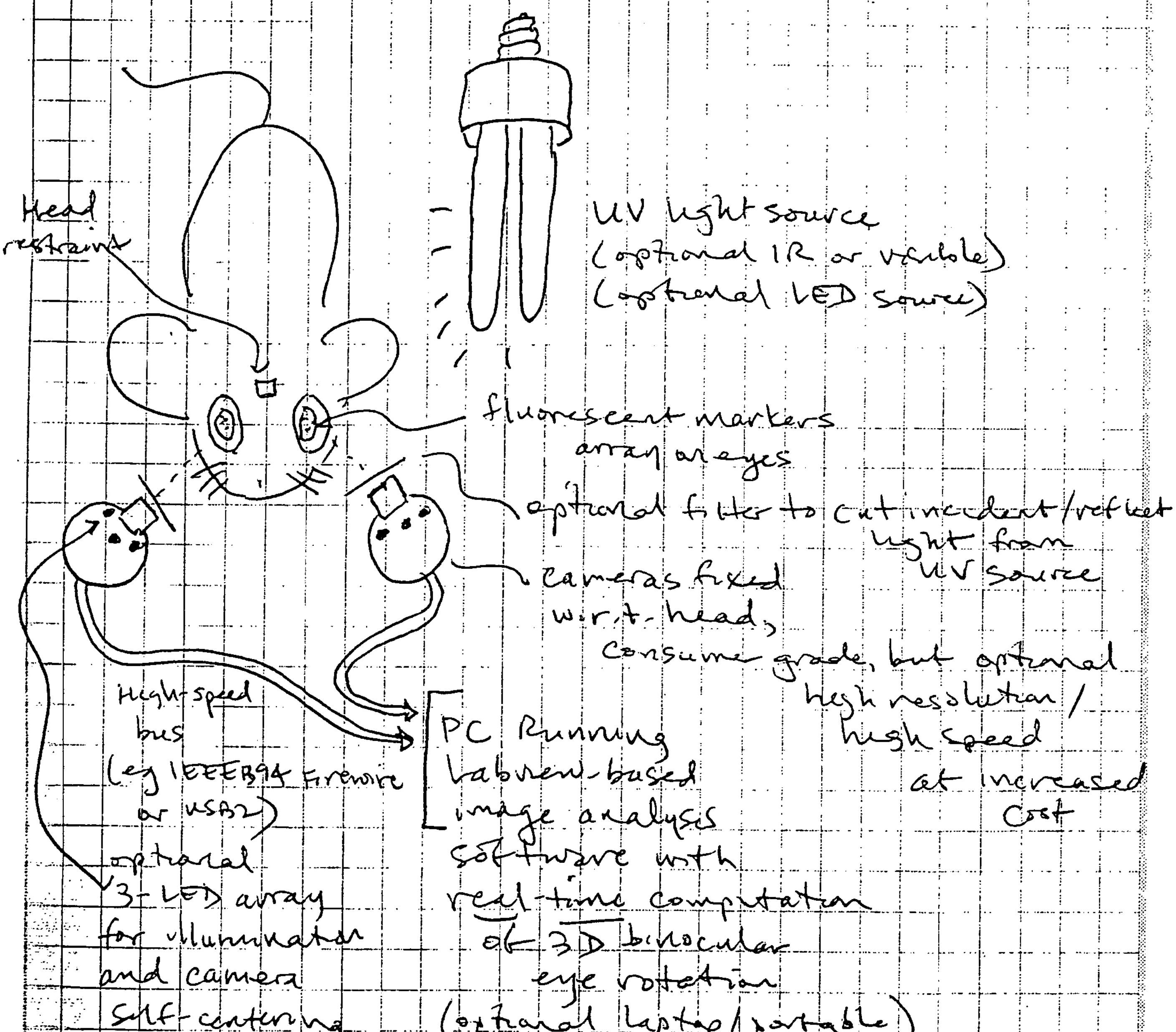

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